Applicant: Teva Pharmaceuticals (Pty) Ltd.	Product name: ANASTROZOLE 1 mg TEVA
Registration No.: 42/21.12/0760	**Dosage Form:** Each film-coated tablet contains 1 mg anastrozole

PROFESSIONAL INFORMATION:

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

ANASTROZOLE 1 mg TEVA (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each film-coated tablet contains 1 mg anastrozole.

ANASTROZOLE 1 mg TEVA contains sugar: (87,00 mg lactose monohydrate per film-coated tablet).

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Film-coated tablets.

White to off white, film-coated round shaped tablet. One side of the tablet debossed with the number '93'. The other side of the tablet debossed with the number 'A10'.

4. CLINICAL PARTICULARS:

4.1. Therapeutic indications:

ANASTROZOLE 1 mg TEVA is indicated for the treatment of advanced breast cancer in postmenopausal women. Efficacy has not been demonstrated in oestrogen receptor negative patients unless they have had a previous positive clinical response to tamoxifen.

4.2 Posology and method of administration:

Adults including the elderly:

One 1 mg tablet to be taken orally once a day.

Children:

Not recommended for use in children.

Patients with renal impairment:

No dose change is recommended in patients with mild or moderate renal impairment.

Patients with hepatic impairment:

No dose change is recommended in patients with mild hepatic disease.

4.3. Contraindications:

ANASTROZOLE 1 mg TEVA is contraindicated in:

- Pre-menopausal women.
- Pregnant or lactating women (See **section 4.6**).
- Patients with severe renal impairment (creatinine clearance less than 20 ml/min).
- Patients with moderate or severe hepatic disease.
- Patients with hypersensitivity to anastrozole or to any of the excipients as listed in **section 6.1**.

4.4 Special warnings and precautions for use:

General:

The menopause should be defined biochemically (luteinizing hormone [LH], follicle stimulating hormone [FSH], and/or estradiol levels) in any patient where there is doubt about hormonal status. ANASTROZOLE 1 mg TEVA should not be used in pre-menopausal women. There are no data to support the use of ANASTROZOLE 1 mg TEVA with LHRH analogues.

Co-administration of tamoxifen or estrogen-containing therapies with ANASTROZOLE 1 mg TEVA should be avoided as this may diminish its pharmacological action (see **sections 4.5** and **5.1**).

Effect on bone mineral density:

ANASTROZOLE 1 mg TEVA can increase the risk of fractures, due to the fact that anastrozole lowers circulating oestrogen levels which may cause a reduction in bone mineral density.

Women with osteoporosis or women at risk of osteoporosis should have their bone mineral density formally assessed at the commencement of treatment and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored.

The use of specific treatments, e.g., bisphosphonates, may stop further bone mineral loss caused by ANASTROZOLE 1 mg TEVA in postmenopausal women and could be considered (see **section 4.8**).

Hepatic impairment:

ANASTROZOLE 1 mg TEVA has not been investigated in breast cancer patients with moderate or severe hepatic impairment. Exposure to anastrozole can be increased in subjects with hepatic impairment (see **section 5.2**); administration of ANASTROZOLE 1 mg TEVA in patients with moderate and severe hepatic impairment should be performed with caution (see **section 4.2**).

Renal impairment:

ANASTROZOLE 1 mg TEVA has not been investigated in breast cancer patients with severe renal impairment. Exposure to anastrozole is not increased in subjects with severe renal impairment (GRF < 30 ml/min, see **section 5.2**); in patients with severe renal impairment, administration of ANASTROZOLE 1 mg TEVA should be performed with caution (see **section 4.2**).

Paediatric population:

ANASTROZOLE 1 mg TEVA is not recommended for use in children and adolescents, as safety and efficacy have not been established in this group of patients (see **section 5.1**).

ANASTROZOLE 1 mg TEVA should not be used in boys with growth hormone deficiency in addition to growth hormone treatment. In the pivotal clinical trial, efficacy was not demonstrated and safety was not established (see **section 5.1**). Since anastrozole reduces estradiol levels, ANASTROZOLE 1 mg TEVA must not be used in girls with growth hormone deficiency in addition to growth hormone treatment. Long-term safety data in children and adolescents are not available.

ANASTROZOLE 1 mg TEVA contains lactose:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ANASTROZOLE 1 mg TEVA.

Sodium content:

ANASTROZOLE 1 mg TEVA contains less than 1 mmol sodium (23 mg) per tablet, essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction:

Anastrozole inhibits CYPs 1A2, 2C8/9 and 3A4 in vitro. Clinical studies with antipyrine and warfarin showed that ANASTROZOLE 1 mg TEVA dose did not significantly inhibit the metabolism of antipyrine and R– and S-warfarin indicating the co-administration of ANASTROZOLE 1 mg TEVA with other medicinal products is unlikely to result in clinically significant medicinal product interactions mediated by CYP enzymes.

The enzymes mediating metabolism of anastrozole have not been identified. Cimetidine, a weak, unspecific inhibitor of CYP enzymes, did not affect the plasma concentrations of anastrozole. The effect of potent CYP inhibitors is unknown.

A review of the clinical trial safety database did not reveal evidence of clinically significant interaction in

patients treated with ANASTROZOLE 1 mg TEVA who also received other commonly prescribed medicinal products. There were no clinically significant interactions with bisphosphonates (see **section 5.1**).

Oestrogen-containing therapies should not be co-administered with ANASTROZOLE 1 mg TEVA; concomitant use may diminish the pharmacological action of anastrozole. Tamoxifen should not be co-administered with ANASTROZOLE 1 mg TEVA, as this results in a reduction of anastrozole plasma levels (see **sections 4.4** and **5.1**).

4.6 Fertility, pregnancy and lactation:

Pregnancy:

There are no data from the use of ANASTROZOLE 1 mg TEVA in pregnant women. Studies in animals have shown reproductive toxicity (see **section 5.3**). ANASTROZOLE 1 mg TEVA is contraindicated in pregnant women (see **section 4.3**).

Breastfeeding:

There are no data on the use of ANASTROZOLE 1 mg TEVA during lactation. ANASTROZOLE 1 mg TEVA is contraindicated during breastfeeding (see **section 4.3**).

Fertility:

The effects of ANASTROZOLE 1 mg TEVA on fertility in humans have not been studied.

4.7 Effects on the ability to drive and use machines:

ANASTROZOLE 1 mg TEVA is unlikely to impair the ability of patients to drive and operate machinery. However, asthenia and somnolence have been reported with the use of ANASTROZOLE 1 mg TEVA and caution should be observed when driving or operating machinery while such symptoms persist.

4.8 Undesirable effects:

Summary of the safety profile:

The most frequently reported adverse reactions were headache, hot flushes, nausea, rash, arthralgia, joint stiffness, arthritis, and asthenia.

Tabulated list of adverse reactions:

System organ class	Frequent	Less frequent	Frequency not known
Blood and lymphatic system disorders	-	Anaemia, leukopenia, with or without infection; thromboembolism; thrombophlebitis	-
Metabolism and nutrition disorders	Anorexia; hypercholesterolaemia	Hypercalcaemia (with or without an increase in parathyroid hormone), increased appetite; weight gain	-
Psychiatric disorders	Depression	-	-
Nervous system disorders	Dizziness; headache, somnolence, sensory disturbance (including paraesthesia, taste loss and taste perversion), carpal tunnel	Anxiety; confusion; insomnia; nervousness	Memory impairment

	syndrome*		
Eye disorders	-	-	Dry eye
Vascular disorders	Peripheral oedema; hypertension; flushing; hot flushes	-	-
Respiratory, thoracic and mediastinal disorders	Chest pain; dyspnoea; cough; pharyngitis	Bronchitis; sinusitis or rhinitis	-
Gastrointestinal disorders	Constipation; dry mouth; gastrointestinal disturbances, including abdominal pain, diarrhoea, nausea or vomiting	-	-
Hepato-biliary disorders	Abnormalities in liver enzyme values, increases in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase	Elevated gamma-GT and bilirubin, hepatitis	-

Skin and subcutaneous tissue disorders	Skin rash; sweating; hair thinning (alopecia), allergic reactions	Pruritus, Erythema multiforme, Stevens-Johnson syndrome, angioedema, urticaria and anaphylaxis, cutaneous vasculitis (including some reports of Henoch-Schönlein purpura)**	Lichenoid eruption
Musculoskeletal and connective tissue disorders	Arthralgia/Joint pain/stiffness, myalgia, back and bone pain, bone fractures, arthritis, osteoporosis	Trigger finger	Tendonitis, tendon rupture
Reproductive system and breast disorders	Vaginal bleeding***, vaginal dryness	-	-
General disorders and administration site conditions	Asthenia; pain; pelvic pain	Flu syndrome	-

* Events of Carpal Tunnel Syndrome have been reported in patients receiving ANASTROZOLE 1 mg TEVA treatment in clinical trials in greater numbers than those receiving treatment with tamoxifen. However, the majority of these events occurred in patients with identifiable risk factors for the development of the condition.

** Since cutaneous vasculitis and Henoch-Schönlein purpura was not observed in ATAC, the frequency category for these events can be considered as Less frequent based on the worst value of the point estimate.

***Vaginal bleeding has been reported frequently, mainly in patients with advanced breast cancer during the first few weeks after changing from existing hormonal therapy to treatment with ANASTROZOLE 1 mg TEVA. If bleeding persists, further evaluation should be considered.

In a large phase Ill study conducted in 9 366 postmenopausal women with operable breast cancer treated for 5 years, ischaemic cardiovascular events were reported more frequently in patients treated with ANASTROZOLE 1 mg TEVA compared to those treated with tamoxifen, although the difference was not statistically significant. The observed difference was mainly due to more reports of angina pectoris and was associated with a sub-group of patients with pre-existing ischaemic heart disease.

Thromboembolism, fluid retention and dizziness have also been observed in clinical trials with ANASTROZOLE 1 mg TEVA.

Adverse reactions identified during post-marketing experience:

System organ class	Side effects
	Anorexia; hypercholesterolaemia, hypercalcaemia (with or without an increase in parathyroid hormone)
Nervous system disorders	Headache; carpal tunnel syndrome; somnolence; sensory disturbances (including paraesthesia, taste loss and taste perversion)
Vascular disorders	Hot flushes
Gastrointestinal disorders	Nausea; diarrhoea; vomiting
Hepato-biliary disorders	Increase in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase, Increase in gamma-GT and bilirubin; hepatitis.

Skin and subcutaneous tissue disorders	Rash; hair thinning (alopecia); allergic reactions; urticaria; erythema multiforme; anaphylactoid reaction; Stevens-Johnson syndrome; angioedema
Musculoskeletal and connective tissue disorders	Arthralgia/joint stiffness; arthritis; bone pain; trigger finger; myalgia
Reproductive system and breast disorders	Vaginal dryness; vaginal bleeding
General disorders and administration site conditions	Asthenia

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose:

Refer to side effects for possible symptoms of overdosage. There is limited clinical experience of accidental overdose. In animal studies, ANASTROZOLE 1 mg TEVA demonstrated low acute toxicity. Clinical trials have been conducted with various dosages of ANASTROZOLE 1 mg TEVA, up to 60 mg in a single dose given to healthy male volunteers and up to 10 mg daily given to postmenopausal women with advanced breast cancer; these dosages were well tolerated. A single dose of ANASTROZOLE 1 mg TEVA that results in life-threatening symptoms has not been established. There is no specific antidote to overdosage and treatment must be symptomatic.

In the management of an overdose, consideration should be given to the possibility that multiple agents may have been taken. Emptying the stomach via induction of emesis if the patient is alert is recommended.

Haemodialysis may be helpful because ANASTROZOLE 1 mg TEVA is not highly protein bound. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A 21.12 Hormone inhibitors

Pharmacotherapeutic group: Enzyme inhibitors, ATC code: L02B G03

Mechanism of Action:

Anastrozole is a selective non-steroidal inhibitor of aromatase (oestrogen synthetase) system, which converts adrenal androgens to oestrogens in peripheral tissue. Anastrozole does not possess any progestogenic, androgenic or oestrogenic activity.

5.2 Pharmacokinetic properties:

Anastrozole is rapidly and almost completely absorbed from the gastrointestinal tract, maximum plasma concentrations typically occur within two hours of dosing. Food decreases the rate of absorption. Anastrozole is eliminated slowly with a plasma elimination half-life of 40 to 50 hours. Anastrozole is only 40 % bound to plasma proteins. Anastrozole is metabolised in the liver, and excreted in urine (less than 10 % of the dose), mainly as metabolites. The terminal plasma elimination half-life is about 40 to 50 hours, and steady-state concentrations are achieved after about 7 days in patients receiving once-daily doses.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Tablet core:

lactose monohydrate

povidone

sodium starch glycolate

magnesium stearate

purified water

Film coating:

Opadry 02G28619 containing:

hypromellose 5cP 2910 (E464)

titanium dioxide (E171)

macrogol 6000

macrogol 400

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

3 years

6.4 Special precautions for storage:

Store at or below 25 °C.

Do not remove blisters from carton until required for use.

6.5 Nature and contents of the container:

Transparent PVC/PVdC – Aluminium blister packs of 30 tablets. The blister strips together with a package insert are packaged into an outer cardboard carton.

6.6 Special precautions for disposal and other handling:

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City, Midrand

Gauteng, South Africa, 2090

8. REGISTRATION NUMBERS:

42/21.12/0760

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTORISATION:

Date of registration: 07 December 2012

10. DATE OF THE REVISION OF THE TEXT:

15 September 2026